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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,089	10/04/2005	Mahesh Jayachandra	13860.1USWO	2753

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EXAMINER	
RIDER, LANCE W	

ART UNIT	PAPER NUMBER
4131	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,089	JAYACHANDRA, MAHESH	
	Examiner	Art Unit	
	LANCE RIDER	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *23-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/04/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-28 are currently pending..

Election/Restrictions

Applicant's election without traverse of claims 1-22 in the reply filed on May 8th 2009 is acknowledged.

Information Disclosure Statement

The Information Disclosure Statement (IDS), filed by applicant on August 4th 2005 has been considered by the examiner in the present case.

Priority

This application, filed September 4th 2005 is a national stage entry of PCT/US03/20754 filed on July 2nd 2003 which claims priority from a provisional US patent application 60/39377 filed on July 5th 2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 6 is drawn to a method for treating injury to an excitable tissue in which a non-specific protease inhibitor is administered as an ice-cold perfusate. (Zhang, X., et al. Journal of Neuroscience Methods, 2007) indicates on page 40, in paragraphs 1 and 2, and in paragraphs 1 and 2 of the discussion, that administration of an ice-cold perfusate causes dendritic beading. The discussion also shows in paragraph 6 that this dendritic beading is part of the pathology of the same excitable tissue damages applicant is trying to treat, such as ischemia and traumatic injury. Claim 6 lacks enablement as it would cause excitable tissue damage rather than treat it. This is directly contrary to the treatment of these tissues and would indicate the exact opposite of what applicant claims, and would therefore require significant experimentation to prove the efficacy of the technique in light of the findings of (Zhang, X., et al. Journal of Neuroscience Methods, 2007).

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims is seen to encompass methods for treating excitable tissue with a nonspecific protease inhibitor as an ice cold perfusate. Excitable tissue as described in the instant specification, is seen to include the all tissues with voltage gated ion channels, particularly neural and muscle tissues.

The state of the prior art

The current methods in the art for treatment of excitable tissues by perfusing tissues can be seen in (Zhang, X., et al. Journal of Neuroscience Methods, 2007). A warm perfusate does not cause the dendritic beading

The level of one of ordinary skill

The level of skill is that of a MD or PhD, BS or MS .

The amount of direction provided by the inventor

The examiner notes, there is not seen sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or reference to same in the prior art to provide the skilled artisan with sufficient guidance to practice the instant treatment method. The data and evidence provided in the instant disclosure leads the examiner to doubt the objective truth of assertions of treatment with of an excitable tissue with an ice-cold perfusate.

The existence of working examples

The specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. There is not seen in the disclosure, sufficient evidence to support applicant's claims of prevention. There is not seen sufficient working examples or data from references of the prior art providing a nexus between that which applicant asserts as proof of a method for treating excitable tissue with an ice-cold perfusate or extrapolation from the data and

evidence currently provided on the record to support methods drawn to treating in such a manner.

The quantity of experimentation needed to make or use the invention

The leap to treatment of an excitable tissue with an ice-cold perfusate is not tenable or expected by one of ordinary skill in the art at the time of the invention. (Zhang, X., et al. Journal of Neuroscience Methods, 2007) indicates on page 40, in paragraphs 1 and 2, and in paragraphs 1 and 2 of the discussion, that administration of an ice-cold perfusate causes dendritic beading. The discussion also shows in paragraph 6 that this dendritic beading is part of the pathology of the same excitable tissue damages you are trying to treat, such as ischemia and traumatic injury. This is directly contrary to the treatment of these tissues and would indicate the exact opposite of what applicant claims, and would require significant experimentation to prove the efficacy of the technique in light of the findings of (Zhang, X., et al. Journal of Neuroscience Methods, 2007).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the

prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5, 7-13, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cuckler, J.M. Journal of Bone and Joint Surgery, 1985), in view of (Stracher, A., EP 100673).

Claims 1-5 are drawn to a method for determining whether a subject has suffered an injury to an excitable tissue, administering to the subject a therapeutically effective amount of a sodium channel blocker (procaine), a non-specific protease inhibitor (leupeptin), and a corticosteroid (methylprednisone).

(Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) discloses on page 64 in the methods section, paragraph 1, a method for determining whether a subject has suffered an injury to an excitable tissue including the use of computed tomography, myelography, or epidural venography studies. (Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) also discloses on page 63 in the abstract, and in the methods paragraph 1, the use of procaine and

methylprednisolone (methylprednisone) for the treatment of an excitable tissue (neural tissue).

(Cuckler, J.M. Journal of Bone and Joint Surgery, 1985), does not disclose the treatment with leupeptin. (Stracher, A., EP 100673) discloses on page 3, in the summary of the invention the administration of leupeptin for the treatment of nerve damage.

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In the instant case (Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) has disclosed the use of procaine and methylprednisone for the treatment of nerve damage, and (Stracher, A., EP 100673) has disclosed the use of leupeptin for the treatment of nerve damage. The idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)) **MPEP 2144.06**. It would have been obvious to those of ordinary skill in the art at the time of the invention to combine the methods for determining whether a excitable tissue injury has occurred as disclosed by (Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) along with the use of procaine and methylprednisone as they disclosed with Stracher's disclosure for the treatment of nerve damage with leupeptin.

Claims 7 and 8 are drawn to the administration of the compounds as either a single drug dose or as separate drug dosages. (Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) disclose the use of procaine and

methylprednisolone separate without the inclusion of leupeptin disclosed in (Stracher, A., EP 100673), so it is obvious from the prior art that the administration of the compounds has been performed separately. As both compounds are used to treat the same dysfunction, it would also logically flow that they could be used in combination. The treatment with different drug dosages and their administration together or apart would depend upon the injury being treated, the length of the treatment, and the condition of the patient. The administration of leupeptin can be either parenteral during and after surgical procedures, or in an oral form for longer term treatment, disclosed in (Stracher, A., EP 100673) on page 5, lines 20-34, and page 6, lines 5-16. Depending upon the condition of the patient, the administration of these compounds would obviously depend upon multiple criteria and would have been common decisions for one of ordinary skill in the art at the time of the invention.

Claims 9-13 are drawn to a method of claim 1 stated supra with the further limitations of administering the compounds within a certain time periods and either systemically or in proximity to damaged tissue.

(Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) discloses on page 63 in the abstract, and in the methods paragraph 1, the use of procaine and methylprednisolone (methylprednisone) for the treatment of an excitable tissue. (Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) does not specifically disclose a specific need for the administration of these compounds within a certain time frame or in a certain form.

(Stracher, A., EP 100673) discloses on page 5, lines 20-34, that the most efficient treatment with leupeptin is to treat the injured site as rapidly as possible, anywhere fro immediately out to the 8 hours claimed. (Stracher, A., EP 100673) discloses on page 18, claim 9, that leupeptin can be administered at the site of the injured tissue, and on page 6, lines 1-16 that it can be administered systemically by oral administration.

A mixture of these compounds would have been obvious to one of ordinary skill in the art at the time of the inventions for the reasons cited supra for claims 1-5, the mixtures properties and administration would obviously be dependent upon the properties of each individual component in the mixture. In the instant case leupeptin is known to be more efficacious upon rapid delivery to the injured site, and it would have been obvious to one of ordinary skill in the art at the time of the invention, that the inclusion of this compound would necessitate administration methods which would include its administration in a rapid manner. The systemic or proximal administration of leupeptin was also known, which would effect the administration of the mixture of compounds as well. Depending upon the condition of the patient, the administration of these compounds would obviously depend upon multiple criteria and would have been common decisions for one of ordinary skill in the art at the time of the invention. The administration of the composition more than once as claimed in claim 22, "the reperfusion of the injured tissue" would also have been obvious to one of ordinary skill in the art at the time of the invention depending upon the needs of the patient, such as the

need for further treatment after a previously ineffective administration of the drugs.

Claims 14-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cuckler, J.M. Journal of Bone and Joint Surgery, 1985), in view of (Stracher, A., EP 100673), as applied to claims 1-5, 7-13 and 22 above, and in further view of (Wan, et al., The Journal of Thoracic and Cardiovascular Surgery, 1996), (Sellevold, O.F.M., et al., Cardiovascular Anesthesia, 1995), and (Atsma, D.E., Circulation Research, 1995).

Claims 14-20 are drawn to the treatment of excitable tissues, specifically to the central nervous system, the brain, and the brain due to ischemic damage, tissues damaged by a stroke (namely muscle and nervous tissue), the spinal cord, the heart, and tissues of the heart damaged by myocardial infarction.

(Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) discloses on page 64 in the methods section, paragraph 1, a method for determining whether a subject has suffered an injury to an excitable tissue including the use of computed tomography, myelography, or epidural venography studies. (Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) also discloses on page 63 in the abstract, and in the methods paragraph 1, the use of procaine and methylprednisolone (methylprednisone) for the treatment of an excitable tissue (neural tissue).

(Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) further discloses the use of procaine and methylprednisolone for the treatment of lumbar pain

(spinal cord injury) primarily as a treatment for nervous tissue as stated supra. (Stracher, A., EP 100673) discloses the use of leupeptin for the treatment of nerve injury as stated supra and as a treatment for muscle injury disclosed on page 11, lines 6-9.

(Cuckler, J.M. Journal of Bone and Joint Surgery, 1985) does not specifically disclose the treatment of muscle tissues such as the heart and conditions like ischemia and (Stracher, A., EP 100673) does not disclose specifically the treatment of heart tissue or ischemia with leupeptin.

(Wan, et al., The Journal of Thoracic and Cardiovascular Surgery, 1996) discloses in the abstract, the treatment of heart transplant patients with methylprednisolone therapy, using methylperdnisolone to treat damage to heart tissue which would include damage by a stoke or myocardial infarction. (Sellevold, O.F.M., et al., Cardiovascular Anesthesia, 1995) discloses in the abstract the use of procaine to treat damage to heart tissue (in specific for treating ventricular fibrillation) which would include damage by a stoke or myocardial infarction. (Atsma, D.E., Circulation Research, 1995) discloses the use of leupeptin as a calpain I inhibitor for the treatment of cell death in ischemic hearts, which would include damage by a stoke or myocardial infarction.

All of the drugs procaine, methylprednolisone, and leupeptin have all been disclosed for the treatment of excitable tissues. They have been used in both treatments and therapies for treatment of the heart, muscles, and ischemia, as well as in the treatment of nerve damage including the brain, spinal cord, and central nervous system. The use of these drugs for the treatment of diseases

related to nerve and muscle injury were well known in the art at the time of the invention and would have been obvious therapies for one of ordinary skill in the art at the time of the invention.

One of ordinary skill in the art at the time of the invention would have been motivated to combine methylprednisolone with procaine and leupeptin for the treatment of injuries to both muscle and nervous tissues. It was well known to those of ordinary skill in the art at the time of the invention that ischemia leads to both damage to the heart and to the nervous system. It would have therefore obvious to one of ordinary skill in the art at the time of the invention to combine the known treatments of (Cuckler, J.M. Journal of Bone and Joint Surgery, 1985), in view of (Stracher, A., EP 100673), with the treatments of (Wan, et al., The Journal of Thoracic and Cardiovascular Surgery, 1996), (Sellevold, O.F.M., et al., Cardiovascular Anesthesia, 1995), and (Atsma, D.E., Circulation Research, 1995), to arrive at a treatment for injuries to both muscle and nervous tissue such as found in ischemic patients.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over (Cuckler, J.M. Journal of Bone and Joint Surgery, 1985), in view of (Stracher, A., EP 100673), as applied to claims 1-5, 7-13 and 22 above, and in further view of (Young, W. "Current treatment for Human Spinal Cord Injury", web article included in IDS).

Claim 22 is drawn to the method of claim 1 stated supra which further comprises decompressing the injured tissues. (Cuckler, J.M. Journal of Bone and

Joint Surgery, 1985) and (Stracher, A., EP 100673) disclose the treatment of nerve injury with procaine, methylprednisolone, and leupeptin. They do not disclose the decompression of tissues.

(Young, W. "Current treatment for Human Spinal Cord Injury", web article included in IDS) discloses on page 1, paragraph 6, the decompression of the spinal cord for the treatment of an injured spinal cord.

The combination of the use of agents for treatment of nervous tissues in the treatment of spinal injury and a mechanical surgical treatment for spinal cord injury would have been an obvious combination for one of ordinary skill in the art at the time of the invention. It would be obvious to repair both the physical spinal/bone damage as well as the tissue damage for such an injury.

Conclusion

No claims are currently allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LANCE RIDER whose telephone number is (571)270-1337. The examiner can normally be reached on Monday through Friday, 7:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LANCE RIDER/
Examiner, Art Unit 4131
/Patrick J. Nolan/

Supervisory Patent Examiner, Art Unit 4131